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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/502,283	02/11/2000	Sun Ai Raillard	02-029510US	4948

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EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 02/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/502,283	RAILLARD ET AL.	
	Examiner	Art Unit	
	Jon D Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,12-17,19,20,22-26,72-78,105-110,112-121,123,125 and 126* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 12-17, 19-20, 22-26, 72-78, 1-5-110, 112-121, 123, 125 and 126* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination (RCE)

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/23/04 has been entered. Claims 1-6, 12-17, 19, 20, 22-78 and 81-126 were pending. Applicants canceled claims 7-11, 18, 21, 27-71, 79-104, 111, 122 and 124. In addition, Applicants amended claims 1 and 105. Therefore, claims 1-6, 12-17, 19, 20, 22-26, 72-78, 105-110, 112-121, 123, 125 and 126 are pending and active in the instant application. An action on the merit follows.

Those sections of Title 35, US code, not included in the instant action can be found in previous office actions.

Withdrawn Objections/Rejections

2. All outstanding rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claims Rejections - 35 U.S.C. 102

3. Claims 1-2, 12-16, 17, 19-20, 22, 72-76, 78, 105, 110, 112-115, 120-121, 123 and 126 are rejected under 35 U.S.C. 102(e) as being anticipated by Aebersold et al. (U.S. Pub. No. 2002/0076739).

For ***claims 1-2***, Aebersold et al. (see entire document) disclose analytical reagents and mass spectrometry based methods for the rapid, and quantitative analysis of proteins (e.g., see Aebersold et al., abstract), which anticipates the claimed invention. For example, Aebersold et al. disclose using ESI-MS to screen for β-galactosidase deficiencies in patients that have a lysosomal storage disease (e.g., GM_1-gangliosidosis) wherein the cells from the various patients constitute a gene library (e.g., see Aebersold et al., page 11, column 2, last paragraph; see also page 8, paragraphs marked 80-84 wherein "in vitro" growth is disclosed; see also page 2, column 1, paragraph 2 wherein a point-mutation gene variant library is disclosed, "The method can also be employed to screen for ... site-directed mutation [i.e., gene variants] ... of the cell, tissue or organism from which the sample originated"; see also page 23, Table IV wherein "allelic" gene variants are disclosed such as mut^O and mut^-). In addition, polymorphic gene variants would also be an inherent feature of the disclosure as these are known to occur every 200 to 300 bp. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Aebersold et al. disclose purifying samples using streptavidin-agarose beads, a non-column-separated technique that is not a chromatographic separation step, wherein the purified samples were injected into ESI-MS to detect the presence of one or more

components of interest (e.g., see page 11, paragraph 107-111, especially paragraphs 108 and 111, "A second feature is the use of affinity tagged reagents containing an enzyme substrate which when combined with affinity purification provide for facile capture of enzymatic products from crude biological fluids ... Conjugates 1 and 2 consist of biotin as an affinity tag, which is coupled to sarcosine. Biotin allows highly specific capture of the substrate conjugate through non-covalent binding to streptavidin immobilized on agarose beads (Bayer et al., 1990) β-galactosidase in this case").

For ***claim 2***, Aebersold et al. disclose live cells as required by claim 2 (see Aebersold et al., page 11, column 2, last paragraph).

For ***claims 12, 75 and 123***, Aebersold et al. disclose the use of organic solvents for purification (e.g., see page 5, column 1, last three paragraphs).

For ***claims 13 and 110***, Aebersold et al. teach cell lysates (e.g., see page 3, paragraph 2).

For ***claims 14-16***, Aebersold et al. teach, for example, β-galactosidase and also β-galactosidase substrates (see Aebersold et al., page 11, column 2, last paragraph).

For ***claims 17 and 112***, Aebersold et al. teach attaching a library to streptavidin-agarose beads (see Aebersold et al., page 11, column 2, last paragraph).

For ***claims 19-20, 113-114***, Aebersold et al. disclose the β-galactosidase enzyme with a streptavidin binding affinity tag e.g., conjugates 3 and 4 including biotin and streptavidin (see Aebersold et al., page 11, column 2, last paragraph).

For ***claims 22, 115***, Aebersold et al. disclose quantifying enzyme products and reactants (see Aebersold et al., page 11, column 2, last paragraph; see also page 2, column 2, paragraph 4).

For ***claims 72-73, 120-121***, Aebersold et al. disclose centrifugation (see Aebersold et al., page 7, column 1, paragraph 3; see also page 10, column 1, paragraph 3; see also page 10, column 2, last paragraph).

For ***claim 74***, Aebersold et al. disclose ion-exchange (e.g., see Aebersold et al., page 15, column 2, last paragraph; see also page 17, column 2, first paragraph).

For ***claim 76***, Aebersold et al. disclose solid-phase extraction (e.g., see Aebersold et al., page 19, column 2, last two paragraphs; see also page 20, column 1, paragraph 1; see also Aebersold et al., page 11, column 2, last paragraph).

For ***claims 78 and 126***, Aebersold et al. disclose pooling multiple samples (e.g., see Aebersold et al., page 7, column 1, paragraph 2; see also page 7, column 2, paragraph 4).

For ***claim 105***, Aebersold et al. disclose a gene library that encodes among other enzymes β-galactosidase and N-acetyl-R-D-glucosaminidase from cultured fibroblast obtained from patients with lysosomal storage diseases and also from healthy individuals (see Aebersold et al., page 11, column 2, last paragraph). These samples were purified using a "capture" technique employing streptavidin-agarose beads. Finally, the purified samples were analyzed by ESI.

Response

4. Applicant's arguments directed to the above 35 U.S.C. § 102 rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicants argue, "Aebersold et al. ... do not describe the claimed steps of, for example, providing one or more cell comprising a gene variant library and growing the one or more cell in vitro ... [nor] is a 'gene variant library' [disclosed]" (e.g., see 11/23/04 Response, page 11, last paragraph).

This is not found persuasive for the following reasons:

The Examiner respectfully disagrees. Aebersold et al. describe several different gene libraries including, for example, gene libraries generated via "point mutations" and "allelic variation" (e.g., see newly amended rejection above). In addition, genetic variation would inherently be disclosed by the present invention because the genes would contain polymorphic variation (e.g., see newly amended rejection above). In addition, the Examiner contends that Aebersold et al. disclose "cell cultures" that read on "growing" cells (e.g., see page 11, last paragraph, "In a typical procedure, 0.2 mM 1 and 0.3 mM 2 were incubated with sonicated cultured fibroblasts from individual patients with [beta]-galactosidase deficiency and with fibroblasts cultured from unaffected people. After incubation, labeled internal standards 5 and 6 were added, and the biotinylated components were captured on streptavidin-agarose beads"). In

addition, Aebersold et al. disclose many other examples of "in vitro" growth (e.g., see page 8, paragraphs marked 80-84 wherein *S. cervisae* is grown *in vitro*).

Accordingly, the 35 U.S.C. § 102 rejection cited above is hereby maintained.

Claim Rejections - 35 USC § 103

5. Claims 1-2, 12-17, 19-20, 22-26, 72-76, 78, 105, 110, 112-121, 123 and 126 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aebersold et al. (U.S. Pub. No. 2002/0076739) and Siuzdak et al. (Siuzdak, G. Mass Spectrometry for Biotechnology. New York: Academic Press. 1992).

For ***claims 1-2, 12-16, 17, 19-20, 22, 72-76, 78, 105, 110, 112-115, 120-121, 123 and 126***, Aebersold et al. teach all the limitations stated in the 35 U.S.C. 102(b) rejection above (incorporated in its entirety herein by reference), which anticipates claims 1-2, 12-16, 17, 19-20, 22, 72-76, 78, 105, 110, 112-115, 120-121, 123, 126 and, consequently, also renders obvious claims 1-2, 12-16, 17, 19-20, 22, 72-76, 78, 105, 110, 112-115, 120-121, 123 and 126.

The prior art teaching of Aebersold et al. differs from the claimed invention as follows:

For ***claims 23-26, 116-119***, the prior art teachings of Aebersold et al. differ from the claimed invention be not explicitly reciting the use of "neutral loss" and "parent ion" techniques. Aebersold et al. only described the general use of a triple quadrupole mass

spectrometer and general methods like collision-induced dissociation (e.g., see Aebersold et al., page 19, Exemplary MS^N Techniques and Instrumentation Section).

However, Siuzdak et al. teach the following limitations that are deficient in Aebersold et al.:

For ***claims 23-26, 116-119***, Siuzdak et al. disclose "neutral loss" and "parent ion" techniques are routinely used on "triple quadrupole" mass spectrometers employing "collision induced dissociation" techniques (e.g., see page 100, last paragraph; see also page 120, paragraph 3; see also figure 6.1).

It would have been obvious to one skilled in the art at the time the invention was made to use the method as taught by Aebersold et al. with the "textbook" techniques as taught by Siuzdak et al. because Siuzdak et al. provides the basic background and practical applications of mass spectroscopy including ESI specifically for biotechnology, which would encompass the screening method of Aebersold (i.e., the references represent analogous art). Furthermore, one of ordinary skill in the art would have been motivated to combine Siuzdak with Aebersold et al. because Siuzdak et al. teach that structural information can be obtained for a broad range of systems including enzyme catalysis (e.g., see pages 122-126) and shows in detail how Aebersold et al. could be modified to improve the enzyme catalysis and expand the capabilities of the method to other research areas.

6. Claims 1-6, 12-17, 19-20, 22-26, 72-78, 105-110, 112-121, 123, 125 and 126 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aebersold et al. and Siuzdak et al. (U.S. Pub.

No. 2002/0076739) and Siuzdak et al. (Siuzdak, G. Mass Spectrometry for Biotechnology. New York: Academic Press. 1992) and Weinberg et al. (WO 98/15969).

For ***claims 1-2, 12-17, 19-20, 22-26, 72-76, 78, 105, 110, 112-121, 123 and 126***, the combined teachings of Aebersold et al. and Siuzdak et al. teach all the limitations stated in the 35 U.S.C. 103(a) rejection above (incorporated in its entirety herein by reference), which renders obvious claims 1-2, 12-17, 19-20, 22-26, 72-76, 78, 105, 110, 112-121, 123 and 126.

The combined prior art teaching of Aebersold et al. and Siuzdak et al. differs from the claimed invention as follows:

For ***claims 2-6, 77, 106-109 and 125***, the combined prior art teachings of Aebersold et al. and Siuzdak et al. differ from the claimed invention by not specifically reciting the use of a "100 samples" in "less than an hour". Aebersold et al. teach that their screening method may be readily automated for high throughput, but does not discuss a rate (see Aebersold et al., page 12, column 2, paragraph 1).

However, Weinberg et al. teach the following limitations that are deficient in Aebersold et al. and Siuzdak et al.:

For ***claim 2-6, 77, 106-109 and 125***, Weinberg et al. (see entire document) teach that the "automated" mass spectrometer can reach speed "faster than 10, 1000, or 1000 library elements per second" (see Weinberg et al., page 6, line 28), which would read on 100, 200, 500, 1000 samples in less than an hour.

It would have been obvious to one skilled in the art at the time the invention was represent analogous art i.e., they all encompass the use of electrospray ionization mass

spectroscopy. Furthermore, one of ordinary skill in the art would have been motivated to use the "high throughput methods" as taught by Weinberg et al. with the combined teachings of Aebersold et al. and Siuzdak et al. because more samples could be studied in less time (e.g., see Weinberg et al., page 6, line 28). Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because Aebersold et al. and Siuzdak et al. teach that high throughput methods can be used (see Aebersold et al., page 12, column 2, paragraph 1), which would include the methods of Weinberg et al.

Response

7. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejections were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicants argue, "Siuzdak et al. reference ... actually teach away from the claimed method. The top of page 120 begins, 'CSF analysis began with preparative liquid chromatography fraction collection.' Claims 1 and 105, as amended, specify that the purifying step is not a chromatographic separation step ... Moreover, the Weinberg et al. patent publication does not describe or suggest a method of high throughput mass spectrometry screening that does not utilize chromatography" (e.g., see 11/23/04 Response, page 12, last two paragraphs).

This is not found persuasive for the following reasons:

In response to applicant's arguments against the Weinberg et al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, the combination of references teach the use of high throughput mass spectrometry screening that does not utilize chromatography (e.g., see newly amended rejection above). Thus, attacking the Weinberg et al. reference individually does not amount to a "teaching away" as purported by Applicants because the secondary references (e.g., Weinberg et al.) are not being relied on in their individual capacities to disclose the claimed element. In the present case, the "automation" disclosed by Weinberg et al. would be generally applicable to all electrospray mass spectrometers whether they were using chromatographic separations or not.

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

New Rejections

Claims Rejections - 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. **Claim 12** recites the limitation "said purifying one or more non-column separated samples" in lines 1-2. There is insufficient antecedent basis for this limitation in the claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
February 18, 2005